Curing Lymphomas, One Subtype at a Time

Now a Senior Investigator in CCR's Lymphoid Malignancies Branch, Wyndham Wilson, M.D., Ph.D., came to the NIH as a Clinical Fellow in 1984. After completing fellowships in oncology and infectious disease, Wilson joined NCI's Division of Cancer Treatment, where he began working on improving chemotherapy treatments for aggressive lymphomas. Wilson recruited Kieron Dunleavy, M.D., as a Clinical Fellow in 2002; Dunleavy has gone on to become a Staff Clinician. Working closely with their CCR collaborator, Louis M. Staudt, M.D., Ph.D., Wilson and Dunleavy have continued to optimize therapeutic strategies through clinical trials, which include targeted agents against molecularly differentiated subtypes of diffuse large B-cell lymphomas. Two of their recent trials, published in the New England Journal of Medicine, *had cure rates above 95 percent.*

Wyndham Wilson Throws Down the Gauntlet

My father was an academic physician who did medical research, so I knew I wanted to be an academic doctor since the age of six. My focus on clinical translation—integrating both laboratory and clinical work to make a real difference for patients—evolved with my training.

The backbone chemotherapy for the work we do today really started in 1989. We were trying to understand why people were failing chemotherapy. For the most common type of lymphoma, diffuse large B-cell lymphoma (DLBCL), only 30 percent of patients were being cured. So in collaboration with Tito Fojo, M.D., Ph.D., I developed the DA-EPOCH regimen right after my fellowship as a strategy to overcome the multidrug resistance and to optimize chemotherapy efficacy using continuous infusion schedules.

(Photo: R. Baer)

A patient, Kieron Dunleavy, M.D., Wyndham Wilson, M.D., Ph.D., and members of Wilson's clinical research group, Catherine Lai, M.D., and Mark Roschewski, M.D., having a conference

Building a Backbone

EPOCH consists of multiple chemotherapeutic agents—doxorubicin, vincristine, and etoposide—administered with prednisone and cyclophosphamide. Rather than simply specifying dosages based on amount and dosing schedule, I brought in the concept of pharmacodynamically adjusting the dose (DA-EPOCH), I hypothesized that we could biologically assess drug clearance by monitoring the number of neutrophils in the blood and

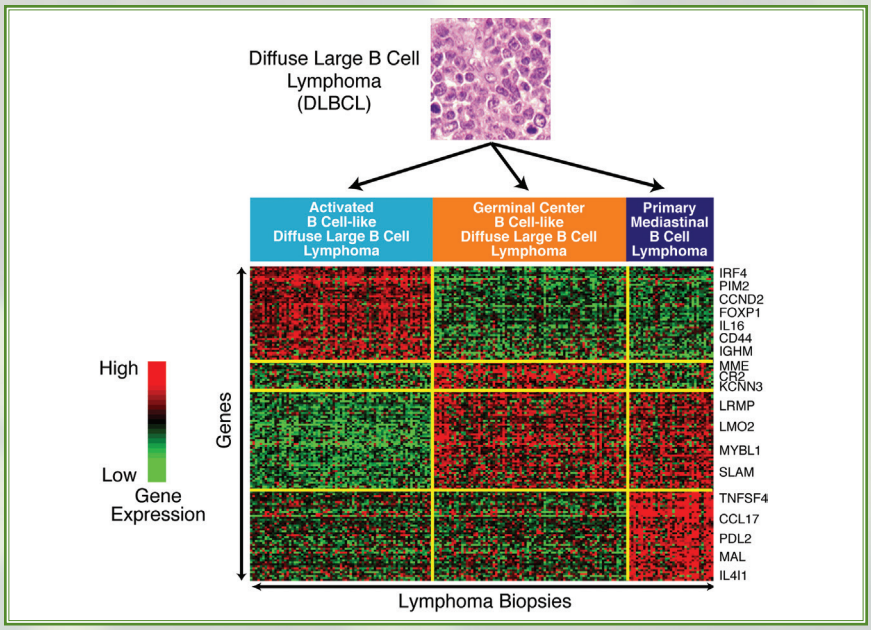
developed a strategy to increase the chemotherapy doses until the neutrophils went below 500 cells. Depending on factors like age and genetics, different dose escalations are necessary to reach that same goal in different patients.

Following the development of rituximab, a monoclonal antibody therapeutic that targets a protein found prominently on the surface of B cells, we incorporated it into DA-EPOCH (DA-EPOCH-R). Based on multiple clinical trials, DA-EPOCH-R appeared to be more effective than the standard of care, R-CHOP (a combination of rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone).

Unfortunately, the history of the field made it difficult to convince the community to adopt DA-EPOCH-R until relatively recently. CHOP was developed in 1975, leading to a rash of published studies from single institutions that tested multiple variants of CHOP that incorporated more drugs, and appeared to be superior to CHOP. However, a randomized study ultimately showed that all these variations were equivalent to the original. Thus, there was a strong burden of proof required to renew optimism in the field.

To further confound the field, Lou Staudt elegantly showed that DLBCLs are not a single tumor type and, moreover, that different subtypes had different outcomes with R-CHOP. Based on this work, we showed that DA-EPOCH-R was particularly effective in specific molecular subtypes of DLBCL and have just completed a large randomized study comparing DA-EPOCH-R and R-CHOP within the molecular subtypes of DLBCL.

We have not only worked to improve efficacy, but also to limit the toxic side effects of treatment. We published two papers in the *New England Journal of Medicine*, testing DA-EPOCH-R in two subtypes of DLBCL: primary mediastinal B-cell lymphoma and Burkitt lymphoma. In the first, we were able to eliminate radiation therapy and in the second, we were able to substantially lower the amount and duration of chemotherapy while achieving long-term remissions and likely cure rates in approximately 95 percent of patients.



(Figure: L. Staudt, CCR)

Biopsies of diffuse large B cell lymphoma (DLBCL) reveal varying gene expression levels in activated B cell-like DLBCL, germinal center B cell-like DLBCL, and primary mediastinal B cell lymphoma.

ABCs of Lymphoma

Lou and I met around the late 1990s, here at NCI. Interestingly, we were both in the M.D./Ph.D. Medical Science Training Program, which is sponsored by the Federal Government to train medical scientists—I was at Stanford and he was at the University of Pennsylvania. While I focused on clinical research, Lou pursued basic laboratory research, but we were both working on lymphoid tumors so it was a very logical thing to work together. He wanted to see his discoveries translated into therapeutic advances for patients, and I wanted to understand and advance the fundamental science underpinning our work. It really was a synergistic situation and today, our groups work closely together.

One of the subtypes of DLBCL identified by Lou's laboratory—activated B cell-like (ABC)—has notably poor outcomes. Lou has identified a number of the molecular abnormalities and affected signaling pathways in ABC, so we have been working on a series of studies using drugs to block activation of these pathways.

In 2009, we published a paper in *Blood*, in which we showed that bortezomib increases the sensitivity of the ABC subtype to chemotherapy. Bortezomib is an inhibitor of the proteasome, which normally degrades cellular proteins. In particular, we were interested in stopping the degradation of IκBα, an inhibitor of the NF-κB pathway, which Lou's laboratory has found is constitutively active in ABC DLBCL. Based on our results, Millennium Pharmaceuticals, which produces bortezomib under the trade name Velcade, has started a large clinical trial looking at this drug in ABC DLBCL.

> ...we can now cure most high grade, B-cell lymphomas.

We also did a study with the drug ibrutinib (Imbruvica), a potent inhibitor of Burton's tyrosine kinase (BTK), in DLBCL. BTK is a prominent signaling molecule in the NF-κB pathway. Based on our findings, Pharmacyclic's partner Janssen, is sponsoring a large international randomized clinical trial with 800 patients to develop this drug in a combination therapy for patients with newly diagnosed ABC DLBCL.

As we dig deeper, we see that there are specific constellations of mutations that probably require different therapeutic strategies. Ultimately, for precision medicine to be successful, we need to develop the molecular tests to identify targets and combine those with the treatments in clinical trials. Lou and I have done that twice now and it's quite challenging. As we get into smaller molecular subsets, it becomes labor intensive and ultimately, a drug company needs to step in and sponsor a large trial with a companion diagnostic.

With the strategies that we are pursuing here at NCI and the work that is ongoing worldwide, we can now cure most high grade, B-cell lymphomas. When we started, we were lucky if we could cure one in three. So, that's exciting and gratifying. But, other cancers have not fared so well. One of the most exciting things we are working on currently is a new program to treat primary central nervous system lymphomas (PCNSL), which is being led by my colleague, Kieron Dunleavy.

Kieron Dunleavy Takes Up the Challenge

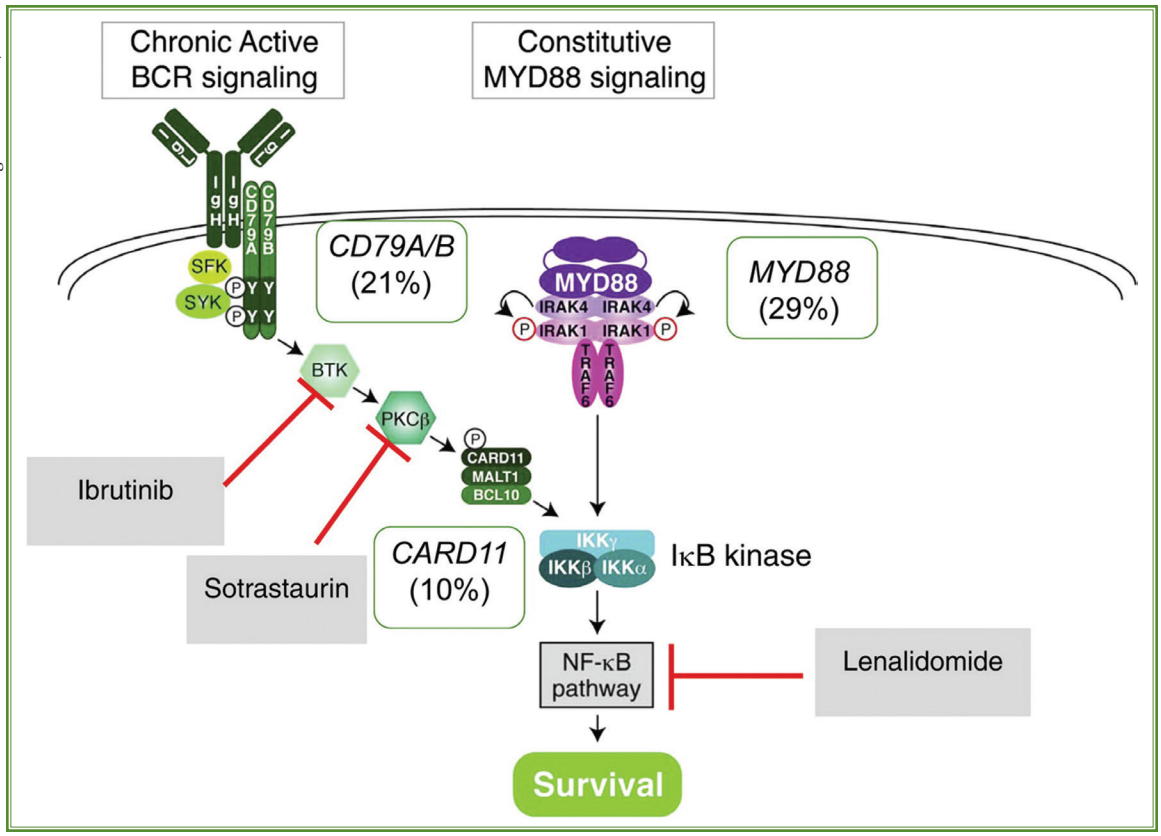
After finishing my medical oncology training in Dublin, Ireland, I was interested in coming to NCI for a medical oncology fellowship because I wanted to focus on innovative clinical and translational research. Working with Wyndham Wilson and collaborating with Lou Staudt, much of the work that I have been involved with focuses on developing novel rational strategies for the treatment of various subtypes of aggressive lymphoma, as for example, in our work with modulators of the NF-κB pathway.

When I first joined CCR, different subtypes of large cell lymphomas had been described, but developing therapies within molecular subtypes had not been done. With Wyndham and Lou, we performed a study in relapsed and refractory DLBCL using bortezomib with chemotherapy and incorporated gene expression profiling. Our hypothesis was that bortezomib would inhibit NF-κB and we would see preferential activity in the ABC subtype (where NF-κB is constitutively activated) as compared to the germinal center B cell-like (GCB) subtype. We did observe a much higher response and survival rate in the ABC subtype in this proof-of-principle study, suggesting that preferentially targeting of a molecular subtype of DLBCL was possible. There are now ongoing randomized studies testing bortezomib in newly diagnosed patients with DLBCL.

Wyndham and Lou led a multi-institutional trial in systemic, relapsed diffuse large cell lymphoma that was just completed and demonstrated that the BTK-inhibitor, ibrutinib (imbruvica), is effective as a single agent in a significant proportion of ABC lymphomas. This is interesting when thinking about new ways to tackle PCNSL. These rare lymphomas constitute just 2–3 percent of all DLBCLs and importantly, outcomes for patients with PCNSL have been inferior to those with systemic DLBCL. There are many reasons for this, including the fact that drugs used in standard DLBCL platforms do not penetrate the blood brain barrier (BBB) very well. As a result, agents that do penetrate the BBB well, such as methotrexate, have typically been used although they have low efficacy and are not routinely used in curable systemic lymphomas.

Recent work has demonstrated that most PCNSLs are of the ABC subtype and frequently harbor specific molecular aberrations that are 'targetable' with small molecule inhibitors. Based on its activity in systemic DLBCL, we hypothesized that ibrutinib could be effective in primary CNS lymphoma. We therefore designed a study that incorporated ibrutinib into a novel immunochemotherapeutic platform of drugs: TEDDI-R (Temozolomide, etoposide, doxil, dexamthasone, ibrutinib, and rituximab). The study is constructed so that there is a so called 'window' in which ibrutinib is tested as a single agent and various imaging and molecular analyses are performed within this period before the start of chemotherapy. Albeit early days in our study, the first two patients treated have demonstrated good responses and this is encouraging.

(Figure: L. Staudt, CCR)



The NF-κB pathway is activated through B-cell receptor signaling in activated B cell-like diffuse large B-cell lymphoma (ABC DLBCL). The mechanisms triggering activation may vary among tumors, and the position of molecular mutations in the tumors plays a role in treatment.

Low-Intensity Therapies in Aggressive Lymphomas

Our group also has a big interest in developing therapies for aggressive B-cell lymphomas that harbor a *MYC* rearrangement. Last year, we published a study demonstrating that in Burkitt lymphoma, DA-EPOCH-R was a highly effective treatment with very low toxicity. This represented a significant departure from standard Burkitt lymphoma strategies that are dose intense and are very toxic for patients, especially those who are older or immunosuppressed. To validate our single-center findings, we are currently doing a multicenter risk-adapted study of the regimen in Burkitt lymphoma. As the regimen was so effective in Burkitt lymphoma, we retrospectively analyzed the outcome of our DLBCL cases that harbored a *MYC*-rearrangement (about 10 percent of all DLBCL) following DA-EPOCH-R. In contrast to the experience with R-CHOP (where *MYC* portends a poor outcome), patients whose tumors had a *MYC* rearrangement had a similar outcome to those without it. Hence, we have an arm in our multicenter study that will specifically evaluate the outcome of *MYC*-rearranged DLBCL cases with DA-EPOCH-R. Considering that R-CHOP is not effective for a high proportion of these patients, our multicenter results will be interesting. (See "On the Other Side of Cancer.")

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To learn more about Dr. Wilson's research, please visit his CCR website at https://ccr.cancer.gov/wyndham-wilson.

To learn more about Dr. Dunleavy's research, please visit his CCR website at https://ccr.cancer.gov/kieron-m-dunleavy.